II. REMARKS:

A. Status of the Claims

Claims 1 and 2 were originally filed with the case. Both claims are rejected in the Office Action mailed on May 30, 2006. Claim 1 is amended, claim 2 is canceled, and claims 3-18 are added herein. Support for the amendments to claim 1 can be found in the specification and in claim 2 as originally filed. Support for the added claims can be found throughout the specification, particularly at page 3, lines 16-35; page 4, lines 4-11;and Examples 1-5. Thus, claims 1 and 3-18 are currently pending.

B. The Objection to Claim 2 is Moot

The Action objects to claim 2 as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Action argues that anecortave acetate is itself a glucocorticoid, and therefore, adding it to the composition of claim 1 does not further limit claim 1. Although Applicants' disagree with the Action's premise, it is believed that the objection has been rendered moot by virtue of the incorporation of the subject matter of claim 2 into claim 1.

C. The Claims Are Definite

Next, the Action rejects the claims under §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Action asserts that the phrases "free of classical preservatives" and "glucocorticoid" are not clearly defined in the specification. Applicants respectfully traverse.

The Action argues that the phrase "free of classical preservatives" is not clearly defined in the specification. According to the Action, a "multitude" of preservatives are known in the art and the specification does not provide guidance with respect to which

preservatives are excluded. The specification explains that the formulations of the invention are "purified, non-preserved glucocorticoid formulations." (Page 3, line 38 to page 4, line 2; emphasis added). Furthermore, the phrases "free of preservatives," or "preservative-free," have meanings that are well-known to one skilled in the art of preparation of ophthalmic formulations. The Action reasons that sodium chloride is a well known preservative and, since all of the examples include sodium chloride, it would not be clear to the skilled artisan which preservatives to include. It is submitted that one skilled in the art of preparation of ophthalmic formulations is aware that sodium chloride is typically used in ophthalmic formulations as an osmolality adjusting agent and not as a preservative.

The Action further asserts that the term "glucocorticoid" is unclear. According to the Action, anecortave acetate is a glucocorticoid, and there are conflicting reports in the prior art regarding the glucocorticoid activity of compounds. Anecortave acetate is a chemical derivative of cortisol designed to enhance angiostatic activity without exhibiting glucocorticoid activity. Although glucocorticoids are well known for their anti-inflammatory and angiostatic activities, they have serious side effects including the development of ocular hypertension and glaucoma in susceptible individuals (Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol 2000;11:478-83). Three modifications were made to cortisol to generate anecortave acetate. The 11β-hydroxyl, essential for glucocorticoid activity, was removed; a double bond was added between C-9 and C-11 to prevent *in vivo* enzymatic rehydroxylation at C-11; and an acetate was added at C-21 to enhance ocular penetration. These chemical modifications have generated a new class of compounds, called cortisenes because replacement of cortisol's 11β-hydroxyl ("ol) with a C9-11 double bond ("ene") forms a cortisene.

The use of the term "glucocorticoid" in the specification is consistent with the normal use of the term by the skilled artisan. Furthermore, the specification distinguishes between anecortave acetate, which lacks typical glucocorticoid activity, and other glucocorticoids. For example, the summary states that the invention is directed to the treatment of persons suffering from retinal edema or NPDR with a glucocorticoid alone or in combination with anecortave acetate. (Page 3, lines 3-5, emphasis added). This use of the term "glucocorticoid" clearly indicates that anecortave acetate is not considered a typical glucocorticoid. Moreover, it is believed that the amendment to claim 1 and the cancellation of claim 2 address the Action's concerns in this respect.

In light of the foregoing arguments, Applicants respectfully request that the definiteness rejections be withdrawn.

D. The Claims are Patentable Over Co-pending Application No. 10/545,055

The Action provisionally rejects claim 2 under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of co-pending application no. 10/545,055. Co-pending application 10/545,055 stems from the same provisional application as the present application. The co-pending application is a 371 application of PCT/US2004/003138, filed February 4, 2004. Applicants understand that the rejection is provisional because the claims of the co-pending application have not yet issued. Applicants intend to modify the claims in the co-pending application to pursue additional subject matter discussed in the specification.

E. Terminal Disclaimers Will Establish the Patentability of the Claims Over Co-pending Application Nos. 10/545,053 and 10/772,963

The Action rejects claims 1 and 2 on the ground of nonstatutory obviousness-type double patentable as being unpatentable over claims 1 and 2 of co-pending application no. 10/545,053 in view of Penn *et al.* The '053 application is directed to the use of

glucocorticoids and anecortave acetate for the treatment of pathologic ocular angiogenesis and any associated edema. Claim 2 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of co-pending application 10/772,963 in view of Penn. The -963 application is directed to the treatment of pathologic ocular angiogenesis and associated edema by administration of compositions containing a glucocorticoid and anecortave acetate. Penn is said to show that diabetic retinopathy is an angiogenic ocular condition. Applicants respectfully traverse.

The posterior segment neovascularization (PSNV) found in exudative AMD is characterized as pathologic choroidal NV, whereas proliferative diabetic retinopathy (PDR) exhibits preretinal NV. Pathologic ocular angiogenesis, which includes PSNV, occurs as a cascade of events that progress from an initiating stimulus to the formation of abnormal new capillaries. Treatments for PSNV and PDR differ. Approved treatments for the PSNV in exudative AMD include laser photocoagulation and photodynamic therapy with Visudyne®; both therapies involve laser-induced occlusion of affected vasculature and are associated with localized laser-induced damage to the retina. For patients with PDR, grid or panretinal laser photocoagulation and surgical interventions, such as vitrectomy and removal of preretinal membranes, are the only options currently available. Thus, it is submitted that treatments for diabetic retinopathy will not necessarily be effective for treating all pathologic ocular angiogenesis in general.

Nevertheless, Applicants agree to submit terminal disclaimers over the '053 and '963 applications as prosecution in the present case progresses toward allowance.

F. <u>The Claims are Patentable Over Martidis, Norden, and Jonas</u>

The Action rejects claim 1 as being anticipated by Martidis, Norden or Jonas. Martidis is said to teach the use of triamcinolone acetonide in patients with nonproliferative

diabetic retinopathy. Norden is said to teach the use of prednisolone acetate for the treatment of retinal edema. Jonas is said to teach the use of cortisone for the treatment of nonproliferative diabetic retinopathy. Applicants respectfully traverse.

It is well settled that in order to support a rejection under section 102, a reference must show ***all*** features of the rejected claim(s). *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1569, 24 USPQ2d 1321 (Fed. Cir. 1992). The Federal Circuit has stated that "absence of a claim element from a prior art reference negates anticipation." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). The present invention is directed to the use of a combination of glucocorticoid and anecortave acetate to treat a person suffering from retinal edema or nonproliferative diabetic retinopathy. None of the cited references discuss the use of anecortave acetate in combination with a glucocorticoid to treat such retinal disorders. Since each cited references lacks a teaching of at least one element of the claimed invention, it is submitted that none of the cited references can anticipate the claimed invention.

In light of the foregoing arguments, Applicants respectfully request that the anticipation rejections based on Martidis, Norden and Jonas be withdrawn.

G. <u>The Claims are Patentable Over Clark</u>

Claims 1 and 2 are rejected as being anticipated by Clark. Clark is said to teach the use of angiostatic steroids for the treatment of any ocular neovascularization including diabetic retinopathy. Clark is further said to teach the use of anecortave acetate and the glucocorticoid tetrahydrocortisol for the prevention of ocular neovascularization. Applicants respectfully traverse.

The Action refers to claim 1 in Clark to support its position that Clark teaches the use of anecortave acetate and tetrahydrocortisol for the prevention of ocular neovascularization. Clark claim 1 is directed to the treatment of ocular neovascularization using a combination of photodynamic therapy (PDT) and a compound selected from a group of compounds that includes anecortave acetate and tetrahydrocortisol. Clark discusses the use of certain compounds, such as anecortave acetate, in combination with PDT, but does not discuss the use of a glucocorticoid and anecortave acetate *per se* for the treatment of such disorders. The portion of the Clark reference relied upon by the Action does not discuss the use of anecortave acetate and tetrahydrocortisol in combination. Rather, it discusses the use of either one of those compounds in combination with PDT. Therefore, it is submitted that the Clark references lacks a teaching of at least one element of the claimed invention.

In light of the foregoing arguments, Applicants respectfully request that the anticipation rejection based on Clark be withdrawn.

H. The Claims are Patentable Over Penn in view of Jonas

Finally, the Action rejects claims 1 and 2 as being unpatentable over Penn in view of Jonas. Penn is said to teach the use of angiostatic steroids, particularly anecortave acetate, to treat angiogenic ocular conditions, including diabetic retinopathy. Penn is said to show the use of a 10% suspension of anecortave acetate. Jonas is said to teach the use of cortisone to treat nonproliferative diabetic retinopathy. The Action acknowledges that neither Penn nor Jonas expressly teaches that the combination of a glucocorticoid and anecortave acetate is useful in a method to treat diabetic retinopathy or retinal edema. Nevertheless, the Action asserts that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a glucocorticoid in combination with anecortave acetate for

the treatment of nonproliferative diabetic retinopathy "to optimize the effective amounts of active agents in the composition to be administered." Applicants respectfully traverse.

The Action simply concludes that "one having ordinary skill in the art at the time the invention was made would have been motivated to employ a glucocorticoid such as cortisone with anecortave acetate for the treatment of nonproliferative diabetic retinopathy." The idea of combining the two compositions is said to flow logically from the compositions having been individually taught in prior art.

Determining obviousness requires an analysis of the invention *as a whole*. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). Significantly, *Gillette* emphasizes that whether all of the elements of the claimed invention were old in other contexts is immaterial to the issue of obviousness. Rather, "*what must be found obvious to defeat the patent is the claimed combination." Id* (quoting *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448, 223 U.S.P.Q. 603, 609-10 (Fed. Cir. 1984)) (emphasis in original).

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or

modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

Moreover, the Board of Patent Appeals and Interferences has held that the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish obviousness. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (BPAI 1993). Section 2143.01 of the MPEP explains the *Levengood* holding as follows:

A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.

MPEP § 2143.01, page 2100-91 (emphasis in original).

The present invention is directed to a method for treating a person suffering from retinal edema or nonproliferative diabetic retinopathy by administering a formulation free of classical preservatives and containing a glucocorticoid and anecortave acetate. Neither Penn nor Jonas discusses preservative free compositions. The Action acknowledges that neither Penn nor Jonas contains a suggestion to combine their teachings. The Action has provided no motivation for the combination of Penn and Jonas, other than to say that it would have been obvious to do so. It is submitted that this bare statement, without an explanation of motivation, is not enough to establish a prima facie case of obviousness. Moreover, even if one would combine the teachings of Penn and Jonas, one would not arrive at the claimed

invention, which requires the use of a preservative-free formulation of a glucocorticoid and anecortave acetate.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection based on Penn and Jonas be withdrawn.

I. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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